(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 January 2004 (15.01.2004)

PCT

(10) International Publication Number
WO 2004/004733 A1

(51) International Patent Classification[7]: A61K 31/519, C07D 487/04, 471/04, A61P 3/04, 25/20

(21) International Application Number: PCT/EP2003/007297

(22) International Filing Date: 8 July 2003 (08.07.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PCT/EP02/07608 9 July 2002 (09.07.2002) EP

(71) Applicant *(for all designated States except US)*: **ACTELION PHARMACEUTICALS LTD.** [CH/CH]; Gewerbestrasse 16, CH-4123 Allschwil (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **AISSAOUI, Hamed** [FR/FR]; 04, Allée des Griottes, F-68840 Pulversheim (FR). **CLOZEL, Martine** [FR/CH]; Winterhalde 3b, CH-4102 Binningen (CH). **FISCHLI, Walter** [CH/CH]; Obertorweg 64, CH-4123 Allschwil (CH). **KOBERSTEIN, Ralf** [DE/DE]; Bergstrasse 34 b, 79539 Lörrach (DE). **SIFFERLEN, Thierry** [FR/FR]; 6, rue de Thann, F-68116 Guewenheim (FR). **WELLER, Thomas** [CH/CH]; Hoelzlistrasse 58, CH-4102 Binningen (CH).

(74) Agent: **HOFMANN, Dieter**; StratAll, Therwilerstr. 87, CH-4153 Reinach (CH).

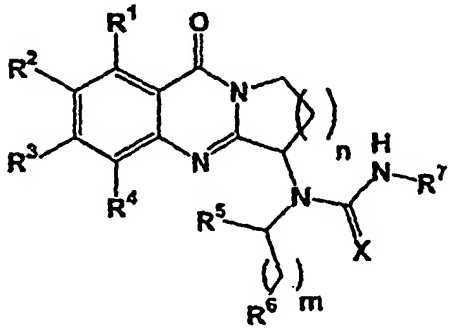
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: 7,8,9,10-TETRAHYDRO-6H-AZEPINO, 6,7,8,9-TETRAHYDRO-PYRIDO AND 2,3-DIHYDRO-2H-PYRROLO[2,1-B]-QUINAZOLINONE DERIVATIVES



(I)

(57) Abstract: The invention relates to novel 7,8,9,10-tetrahydro-6*H*-azepino, 6,7,8,9-tetrahydro-pyrido and 2,3-dihydro-2*H*-pyrrolo[2,1-b]-quinazolinone derivatives of formula (I) and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as orexin receptor antagonists.

WO 2004/004733 A1

ACTELION 22A/OR3

7,8,9,10-Tetrahydro-6*H*-azepino, 6,7,8,9-tetrahydro-pyrido and 2,3-dihydro-2*H*-pyrrolo[2,1-*b*]-quinazolinone derivatives

The present invention relates to novel 7,8,9,10-tetrahydro-6*H*-azepino, 6,7,8,9-tetrahydro-pyrido and 2,3-dihydro-2*H*-pyrrolo[2,1-*b*]-quinazolinone derivatives of the general formula I and their use as pharmaceuticals. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula I, and especially their use as orexin receptor antagonists.

The orexins (hypocretins) comprise two neuropeptides produced in the hypothalamus: the orexin A (OX-A) (a 33 aminoacid peptide) and the orexin B (OX-B) (a 28 aminoacid peptide) (Sakurai T. *et al.*, **Cell**, 1998, 92, 573-585). Orexins are found to stimulate food consumption in rats suggesting a physiological role for these peptides as mediators in the central feedback mechanism that regulates feeding behavior (Sakurai T. *et al.*, **Cell**, 1998, 92, 573-585). On the other hand, it was also proposed that orexins regulate states of sleep and wakefulness opening potentially novel therapeutic approaches for narcoleptic patients (Chemelli R.M. *et al.*, **Cell**, 1999, 98, 437-451). Two orexin receptors have been cloned and characterized in mammals. They belong to the superfamily of G-protein coupled receptor (Sakurai T. *et al.*, **Cell**, 1998, 92, 573-585): the orexin-1 receptor (OX_1) is selective for OX-A and the orexin-2 receptor (OX_2) is capable to bind OX-A as well as OX-B.

Orexin receptors are found in the mammalian host and may be responsible for many biological functions such as pathologies including, but not limited to, depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis; depressive neurosis; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; schizophrenia; manic depression; delerium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Tourette syndrome; feeding disorders such as anorexia, bulimia, cachexia and obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's disease; Cushing's syndrome/disease; basophil adenoma; prolactinoma;

hyperprolactinemia; hypopituitarism; hypophysis tumor/adenoma; hypothalamic diseases; inflammatory bowel disease; gastric diskinesia; gastric ulcus; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; pituitary growth hormone; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; sleep disturbances associated with deseases such as neurological disorders, neuropathic pain and restless leg syndrome; heat and lung diseases, acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardinal infarction; ischaemic or haemorrhagic stroke; subarachnoid haemorrhage; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia, and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndrome I and II; arthritic pain; sports injury pain; pain related to infection e.g. HIV, post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; conditions associated with visceral pain such as irritable bowel syndrome, migraine and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and neurodegerative disorders including nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration epilepsy; seizure disorders and other diseases related to orexin.

The present invention provides 7,8,9,10-tetrahydro-6*H*-azepino, 6,7,8,9-tetrahydro-pyrido and 2,3-dihydro-2*H*-pyrrolo[2,1-*b*]-quinazolinone derivatives which are non-peptide antagonists of human orexin receptors. In particular, these compounds are of potential use in the treatment of obesity and/or sleep disorders.

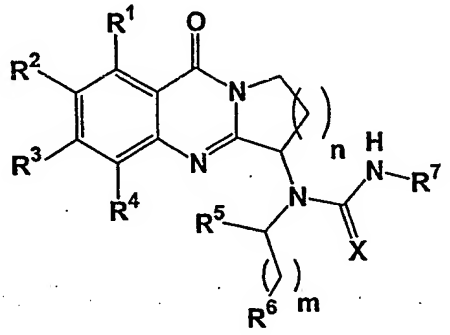
International Patent Applications WO099/09024, WO099/58533, WO00/47577, WO00/47580, disclose phenyl urea derivatives and WO00/47576, discloses quinolinyl cinnamide derivatives as orexin antagonists.

Furthermore, WO 0196302 has been published wherein piperidine derivatives as OX_1 and OX_2 antagonists are disclosed and WO 0185693 has been published wherein N-

acyltetrahydroisoquinoline derivatives as selective OX_2 antagonists are disclosed. In addition, WO 0244172 describes morpholine derivatives as antagonists of orexin receptors.

The novel compounds of the present invention belong to an entirely different class of low molecular weight compounds as compared to all prior art orexin receptor antagonists so far published.

The present invention relates to novel 7,8,9,10-tetrahydro-6*H*-azepino, 6,7,8,9-tetrahydro-pyrido and 2,3-dihydro-2*H*-pyrrolo[2,1-*b*]-quinazolinone derivatives of the general formula (I).



Formula (I)

wherein:

X is O or S;

n is the integer 1, 2, or 3;

m is the integer 0, 1, 2, 3;

R^1, R^2, R^3, R^4 independently represent cyano, nitro, halogen, hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, trifluoromethyl, trifluoromethoxy, cycloalkyloxy, aryloxy, aralkyloxy, heterocyclyloxy, heterocyclyl-lower alkyloxy, R^8CO-, $NR^9R^{10}CO$-, $R^9R^{10}N$-, R^8OOC-, R^8SO_2NH-, R^{11}-CO-NH- or R^2 and R^3 together or R^1 and R^2 together or R^3 and R^4 together

may form with the phenyl ring a five, six or seven-membered ring containing one or two oxygen atoms which are separated by at least one carbon atom;

R^5 represents aryl, aralkyl, lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl;

R^6 represents hydrogen, lower alkyl, trifluoromethyl, $-(CH_2)_m$-OH, $-(CH_2)_m$-O-lower alkyl, $-(CH_2)_m$-CO_2H, $-(CH_2)_m$-CO_2-lower alkyl, $-(CH_2)_m CONH_2$, or $-(CH_2)_m$-CONH-lower alkyl, or $-(CH_2)_m$-CON-(lower alkyl)$_2$, or $-(CH_2)_m$-N-(lower alkyl)$_2$;

R^7 represents aryl, aralkyl, lower alkyl, lower alkenyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl;

R^8 represents lower alkyl, aryl, aralkyl, heterocyclyl or heterocyclyl-lower alkyl;

$R^9$and R^{10} independently represent hydrogen, alkyl, cycloalkyl, cycloalkyl-loweralkyl, aryl, aralkyl, heterocyclyl or heterocyclyl-lower alkyl;

R^{11} represents alkyl, aryl, cycloalkyl, heterocyclyl, $R^9R^{10}N$- or R^8O-.

The compounds of formula I can contain one or more asymmetric centres and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts thereof.

In the present description the term "lower alkyl", alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 8 carbon atoms, preferably a straight or branched-chain alkyl group with 1-5 carbon atoms. Examples of straight-chain and branched C_1-C_8 alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, isobutyl, tert-butyl, the isomeric pentyls, the isomeric hexyls, the isomeric heptyls and the isomeric octyls, preferably methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-butyl, tert-butyl and n-pentyl.

The term "lower alkenyl", alone or in combination, signifies a straight-chain or branched-chain alkenyl group with 2 to 5 carbon atoms, preferably allyl and vinyl.

The term "lower alkoxy", alone or in combination, signifies a group of the formula alkyl-O- in which the term "alkyl" has the previously given significance, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy and tert-

butoxy, preferably methoxy and ethoxy.

Lower alkenyloxy groups are preferably vinyloxy and allyloxy.

The term "cycloalkyl", alone or in combination, signifies a cycloalkyl ring with 3 to 8 carbon atoms and preferably a cycloalkyl ring with 3 to 6 carbon atoms. Examples of C_3-C_8 cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl, preferably cyclopropyl, cyclohexyl or lower alkyl substituted cycloalkyl which may preferably be substituted with lower alkyl such as methyl-cyclopropyl, dimethyl-cyclopropyl, methyl-cyclobutyl, methyl-cyclopentyl, methyl-cyclohexyl, dimethyl-cyclohexyl,

The term "aryl", alone or in combination, signifies a phenyl or naphthyl group which optionally carries one or more substituents, preferably one or two substituents, each independently selected from cyano, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, nitro, trifluoromethyl, trifluoromethoxy, amino, carboxy, alkoxycarbonyl and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-tert-butoxyphenyl, 4-fluorophenyl, 2-chlorophenyl, 4-hydroxyphenyl, 1-naphthyl and 2-naphthyl. Preferred are carboxyphenyl, lower alkoxy-phenyl, hydroxyphenyl and particularly phenyl.

The term "aralkyl", alone or in combination, signifies an alkyl or cycloalkyl group as previously defined in which one hydrogen atom has been replaced by an aryl group as previously defined. Preferred are benzyl and benzyl substituted in the phenyl ring with hydroxy, lower alkyl, lower alkoxy or halogen preferably fluorine. Particularly preferred is benzyl.

For the term "heterocyclyl" and "heterocyclyl-lower alkyl", the heterocyclyl group is preferably a 5- to 10-membered monocyclic or bicyclic ring, which may be saturated, partially unsaturated or aromatic containing for example 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulphur which may be the same or different. Example of such heterocyclyl groups are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, thienyl, thiazolyl, isothiazolyl, furyl, imidazolyl, pyrazolyl, pyrrolyl, indazolyl, indolyl, isoindolyl, isoxazolyl, oxazolyl, quinoxalinyl, phthalazinyl, cinnolinyl, dihydropyrrolyl, pyrrolidinyl, isobenzofuranyl, tetrahydrofuranyl,

dihydropyranyl. The heterocyclyl group may have up to 5, preferably 1, 2 or 3 optional substituents. Examples of suitable substituents include halogen, lower alkyl, amino, nitro, cyano, hydroxy, lower alkoxy, carboxy and lower alkyloxy-carbonyls.

The term "halogen" signifies fluorine, chlorine, bromine or iodine and preferably chlorine and fluorine and particularly fluorine.

The term "carboxy", alone or in combination, signifies a –COOH group.

Preferred compounds are compounds of the general formula I wherein n is the integer 1 or 2, m is the integer 0, 1 or 2, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 have the meaning given in the formula I above and X represents oxygen.

Examples of preferred compounds are:

1-(9-Oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

3-Biphenyl-2-yl-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-Naphthalen-1-yl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-(2-Ethyl-phenyl)-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-(2-Ethoxy-phenyl)-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-(2-Ethyl-phenyl)-1-(6-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-Biphenyl-2-yl-1-(6-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-isopropyl-phenyl)-1-(1-phenyl-ethyl)-urea;

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-naphthalen-1-yl-1(1-phenyl-ethyl)-urea;

1-(7-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(7-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

3-Biphenyl-2-yl-1-(7-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-(2-Ethyl-phenyl)-1-(7-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

1-(6-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-naphthalen-1-yl-1(1-phenyl-ethyl)-urea;

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-isopropyl-phenyl)-1-(1-phenyl-ethyl)-urea;

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

3-Biphenyl-2-yl-1-(7-chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-naphthalen-1-yl-1(1-phenyl-ethyl)-urea;

3-Biphenyl-2-yl-1-(8-chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-isopropyl-phenyl)-1-(1-phenyl-ethyl)-urea;

3-Biphenyl-2-yl-1-(6,7-difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

1-(6,7-Difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

1-(6,7-Difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(6,7-Difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;

3-Biphenyl-2-yl-1-butyl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-urea;

1-Butyl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-n-propyl-phenyl)-urea;

1-Benzyl-3-biphenyl-2-yl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-urea;

1-Benzyl-3-(2-ethoxy-phenyl)-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-urea;

1-Benzyl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3yl)-3-(2-n-propyl-phenyl)-urea;

3-Biphenyl-2-yl-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

3-(2-Ethyl-phenyl)-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

3-(2-Ethoxy-phenyl)-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

3-Naphthalen-1-yl-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

3-Biphenyl-2-yl-1-(2,3-difluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;

1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-3-(2-ethoxy-phenyl)-1-(1-phenyl-ethyl)-urea;

3-Biphenyl-2-yl-1-(3-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

1-(3-Fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

3-(2-Ethoxy-phenyl)-1-(3-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

3-(2-Ethyl-phenyl)-1-(3-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

1-(2-Fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

3-(2-Ethyl-phenyl)-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

1-(2-Fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

3-(2-Ethoxy-phenyl)-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

3-Biphenyl-2-yl-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

1-(2-Fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-3-naphthalen-1-yl-1-(1-phenyl-ethyl)-urea.

Especially preferred compounds are compounds of the general formula I wherein n is the integer 1 or 2, m is the integer 0, R^5 represents methyl, R^6 represents phenyl, R^1, R^2, R^3, R^4, and R^7 have the meaning given in the formula I above and X represents oxygen.

Examples of especially preferred compounds are:

3-Biphenyl-2-yl-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-(2-Ethyl-phenyl)-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-(2-Ethoxy-phenyl)-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-Biphenyl-2-yl-1-(6-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

3-(2-Ethyl-phenyl)-1-(6-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

1-(7-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(6-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-isopropyl-phenyl)-1-(1-phenyl-ethyl)-urea;

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

3-Biphenyl-2-yl-1-(8-chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

1-(6,7-Difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(6,7-Difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;

1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(3-Fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

3-(2-Ethyl-phenyl)-1-(3-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;

1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-3-(2-ethoxy-phenyl)-1-(1-phenyl-ethyl)-urea;

1-(2-Fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

3-(2-Ethyl-phenyl)-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

3-(2-Ethoxy-phenyl)-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

1-(5-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

3-Biphenyl-2-yl-1-(5-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-urea;

1-(5-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

1-(9-Oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

1-(9-Oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

3-(2-Ethyl-phenyl)-1-(9-oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-urea;

3-Biphenyl-1-(9-oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-urea.

Examples of physiologically usable or pharmaceutically acceptable salts of the compounds of formula (I) are salts with physiologically compatible mineral acids such as hydrochloric acid, sulphuric or phosphoric acid; or with organic acids such as methanesulphonic acid, acetic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid. The compounds of formula (I) with free acidic groups can also form salts with physiologically compatible bases. Examples of such salts are alkali metal, alkali earth metal, ammonium and alkylammoniumsalts such as Na, K, Ca or tetraalkylammonium salt. The compounds of formula (I) can also be present in the form of a zwitterion.

The compounds of formula (I) can contain several asymmetric centres and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diasteroisomeric racemates or mixtures of diastereoisomeric racemates and the meso-forms.

Preferred compounds as described above have IC_{50} values below 500 nM; especially preferred compounds have IC_{50} values below 100 nM which have been determinated with the FLIPR (Fluorometric Imaging Plates Reader) method described in the beginning of the experimental section.

The compounds of the general formula (I) and their pharmaceutically usable salts can be used for the treatment of diseases or disorders where an antagonist of a

human orexin receptor is required such as obesity, diabetes, prolactinoma, cardiovascular disorders, cancer, pain, narcolepsy, sleep disorders like insomnia, sleep apnea, parasomnia, depression, anxiety, addictions, schizophrenia, neurodegenerative disorders and dementia.

The compounds of formula (I) and their pharmaceutically usable salts are particularly useful for the treatment of obesity and sleep disorders.

The compounds of formula I may also be used in combination with one or more other therapeutically useful substances e.g. with other orexin receptor antagonists, with lipid lowerer agents, with anorectic agents, with sleep inducing agents, with antidepressants or with other drugs beneficial for the prevention of treatment of obesity or sleep disorders.

The compounds of formula (I) and their pharmaceutically usable salts can be used as medicament (e.g. in the form of pharmaceutical preparations). The pharmaceutical preparations can be administered in enteral or oral form (e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions), nasally (e.g. in the form of nasal sprays) or rectally (e.g. in the form of suppositories). However, the administration can also be effected parentally, such as intramuscularly or intravenously (e.g. in the form of injection solutions).

The compounds of formula (I) and their pharmaceutically usable salts can be processed with pharmaceutically inert, inorganic or organic adjuvants for the production of tablets, coated tablets, dragées, and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc. can be used, for example, as such adjuvants for tablets, dragées, and hard gelatine capsules.

Suitable adjuvants for soft gelatine capsules, are, for example, vegetable oils, waxes, fats, semi-solid substances and liquid polyols, etc.

Suitable adjuvants for the production of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose, etc.

Suitable adjuvants for injection solutions are, for example, water, alcohols,

polyols, glycerol, vegetable oils, etc.

Suitable adjuvants for suppositories are, for example, natural or hardened oils, waxes, fats, semi-solid or liquid polyols, etc.

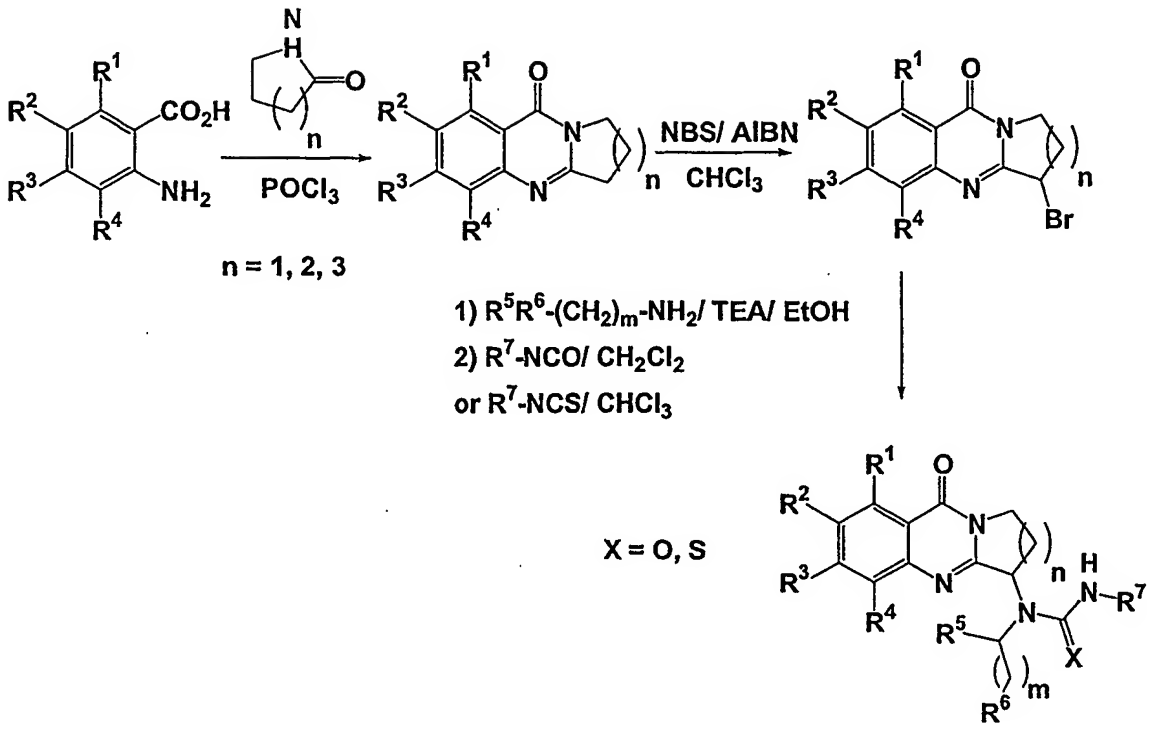
Morever, the pharmaceutical preparations can contain preservatives, solubilizers, viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

The invention also relates to processes for the preparation of compounds of Formula I.

The compounds of general formula (I) of the present invention are prepared according to the general sequence of reactions outlined in the schemes below, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 are as defined in formula (I) above. As the case may be any compound obtained with one or more optically active carbon atom may be resolved into pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates and the meso-forms in a manner known per se.

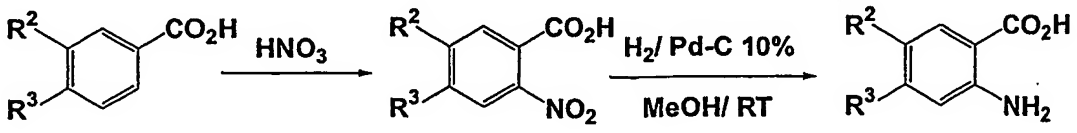
The compounds obtained may also be converted into a pharmaceutically acceptable salt thereof in a manner known per se.

The compounds of general formula (I) may be prepared from the corresponding 2-amino benzoic acid derivatives with the desired lactam by treatment with $POCl_3$ (Karimov A. *et al Chemistry of Natural Compounds* **1982**, 18, 4, 466-472; Bhardwaj V. *et al Indian Journal of Heterocyclic Chemistry* **1999**, 8, 173-176). Subsequent radical bromination (Kamal A. *et al J. Org. Chem.* **2001**, 66, 997-1001) followed by substitution with the corresponding primary amine gave the secondary amine intermediate which is then converted to the desired urea or thiourea compound by reaction with commercially available or synthetized isocyanate or isothiocyanate (Scheme 1) (March J. *Advanced Organic Chemistry-Reactions, Mechanisms and Structure* **1992**, page 418, 4th edition, John Wiley & Sons)



Scheme 1

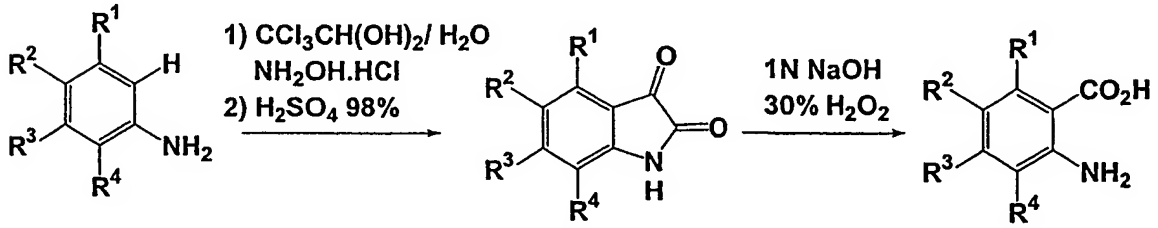
2-Amino benzoic acid derivatives wherein R^1 and R^4 are hydrogen and which are not commercially available might be prepared from benzoic acid derivatives using standard procedures (Giencke A. *et al Liebigs Ann. Chem.* **1990**, 569-579; Follope M.-P. *et al Eur. J. med. Chem.* **1992**, 27, 291-295) as described in Scheme 2.



Scheme 2

Furthermore, 2-amino benzoic acid derivatives may also be prepared from aniline derivatives by reaction with chloral hydrate in the presence of hydroxylamine hydrochloride followed by acidic treatment yielding the isatin intermediate. This was converted to the

corresponding anthranilic acid derivative by reaction with hydrogen peroxide under basic conditions (Scheme 3) (Neal Bramson H. *et al J.Med.Chem.* **2001**, 44, 4339-4358; Deady L.W. *et al J.Med.Chem.* **1997**, 40, 2040-2046; Rowley M. *et al J.Med.Chem.* **1993**, 36, 3386-3396; Hughes P. *et al J.Heterocyclic Chem.* **1990**, 27, 2151-2163).



Scheme 3

Experimental Section

I. Biology

Determination of OX_1 and OX_2 receptor antagonistic activities

The OX_1 and OX_2 receptor antagonistic activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental method:

Intracellular calcium measurements

Chinese hamster ovary (CHO) cells expressing the human orexin-1 receptor or the human orexin-2 receptor, were grown in culture medium (Ham F-12 with L-Glutamine)

containing 300 µg/ml G418, 100 U/ml penicillin, 100 µg/ml streptomycin and 10 % inactivated foetal calf serum (FCS).

The cells were seeded at 80'000 cells / well into 96-well black clear bottom sterile plates (Costar) which had been precoated with 1% gelatine in Hanks' Balanced Salt Solution (HBSS). All reagents were from Gibco BRL.

The seeded plates were incubated overnight at 37°C in 5% CO_2.

Human orexin-A as an agonist was prepared as 1 mM stock solution in methanol: water (1:1), diluted in HBSS containing 0.1 % bovine serum albumin (BSA) and 2 mM HEPES for use in the assay at a final concentration of 10 nM.

Antagonists were prepared as 10 mM stock solution in DMSO, then diluted in 96-well plates, first in DMSO, then in HBSS containing 0.1 % bovine serum albumin (BSA) and 2 mM HEPES.

On the day of the assay, 100 µl of loading medium (HBSS containing 1% FCS, 2 mM HEPES, 5 mM probenecid (Sigma) and 3 µM of the fluorescent calcium indicator fluo-3 AM (1 mM stock solution in DMSO with 10% pluronic acid) (Molecular Probes) was added to each well.

The 96-well plates were incubated for 60 min at 37° C in 5% CO_2. The loading solution was then aspirated and cells were washed 3 times with 200 µl HBSS containing 2.5 mM probenecid, 0.1% BSA, 2 mM HEPES. 100 µl of that same buffer was left in each well.

Within the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices), antagonists were added to the plate in a volume of 50 µl, incubated for 20 min and finally 100 µl of

	IC_{50} (nM)	
	OX_1	OX_2
Example 3	115	79
Example 7	2400	27
Example 28	153	17
Example 30	261	16
Example 33	127	18
Example 40	37	14
Example 41	52	14
Example 44	67	27
Example 49	12	16
Example 50	14	18
Example 51	28	21

Table 1

agonist was added. Fluorescence was measured for each well at 1 second intervals, and the height of each fluorescence peak was compared to the height of the fluorescence peak induced by 10 nM orexin-A with buffer in place of antagonist. For each antagonist, IC_{50} value (the concentration of compound needed to inhibit 50 % of the agonistic response) was determined. The IC_{50} values of selected compounds are given in Table 1.

II. Chemistry

The following examples illustrate the preparation of pharmacologically active compounds of the invention but do not at all limit the scope thereof. All temperatures are stated in °C.

All hydrochloride salts were prepared by dissolving the free-base in dichloromethane and treating with an excess of ethereal HCl (2M).

A. Abbreviations

AIBN	2,2'-azobisisobutyronitrile
BSA	Bovine serum albumine
CHO	Chinese hamster ovary
DMF	Dimethylformamide
eq	equivalent
ES	Electron spray
EtOH	Ethanol
FC	Flash chromatography
FCS	Foetal calf serum
FLIPR	Fluorescent imaging plate reader
HBSS	Hank's balanced salt solution
HEPES	4-(2-Hydroxyethyl)-piperazine-1-ethanesulfonic acid
m	multiplet (NMR)
MeCN	Acetonitrile
MeOH	Methanol
MS	Mass spectroscopy
NBS	*N*-bromosuccinimide
NMR	Nuclear magnetic resonance
LC	Liquid chromatography
q	quartet (NMR)
R_t	retention time

rt	Room temperature
s	singlet (NMR)
t	triplet (NMR)
TEA	Triethylamine
THF	Tetrahydrofuran

B. 2,3-Dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one derivatives

General procedure:

To a mixture of a 2-aminobenzoic acid derivative (1 g), 2-pyrrolidone (1.5 eq), was added carefully $POCl_3$ (2.5 mL). The resulting mixture was stirred at 100°C for 1 h under nitrogen. After cooling, the reaction mixture was poured into ice-water, basified with sat. $NaHCO_3$, extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were dried (anhydrous $MgSO_4$), filtered and concentrated to give a crude brown-yellow viscous oil. FC (CH_2Cl_2/ MeOH: 9/1) afforded the title compound as a solid.

1) 2,3-Dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one

FC (CH_2Cl_2/ MeOH: 9/1) afforded the title compound as a yellow solid (0.97 g, 71%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 2.92 min. *m/z* = 187 (M + 1).
^{1}H-NMR (300MHz; $CDCl_3$) δ 2.2 (2H, m), 3.2 (2H, m), 4.2 (2H, m), 7.4 (1H, t), 7.7 (1H, m), 8.3 (1H, d).

2) 5-Fluoro-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one

FC (CH_2Cl_2/ MeOH: 9/1) afforded the title compound as brown solid (0.92 g, 70%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 3.21 min. *m/z* = 205 (M + 1).
^{1}H-NMR (300MHz; $CDCl_3$) δ 2.3 (2H, q), 3.25 (2H, t), 4.2 (2H, t), 7.4 (2H, m), 8.1 (1H, d).

3) 6-Fluoro-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one

FC (CH_2Cl_2/ MeOH: 9/1) afforded the title compound as yellow crystals (0.79 g, 60%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 3.16 min. *m/z* = 206 (M + 2).
^{1}H-NMR (300MHz; $CDCl_3$) δ 2.3 (2H, q), 3.2 (2H, t), 4.2 (2H, t), 7.15 (1H, m), 7.4 (1H, dd), 8.3 (1H, t).

4) **7-Fluoro-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (CH_2Cl_2/ MeOH: 9/1) afforded the title compound as yellow crystals (0.97 g, 74%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.1 min. *m/z* = 206 (M + 2).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.3 (2H, q), 3.2 (2H, t), 4.2 (2H, t), 7.4 (1H, m), 7.7 (1H, m), 7.95 (1H, dd).

5) **6,7-Difluoro-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (CH_2Cl_2/ MeOH: 9/1) afforded the title compound as orange crystals (0.86 g, 67%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.39 min. *m/z* = 224 (M + 2).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.3 (2H, t), 3.2 (2H, t), 4.2 (2H, t), 7.4 (1H, m), 8.00 (1H, m).

6) **6-Chloro-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (CH_2Cl_2/ MeOH: 9/1) afforded the title compound as yellow crystals (1.11 g, 86%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.55 min. *m/z* = 222 (M + 2).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.3 (2H, q), 3.2 (2H, t), 4.2 (2H, t), 7.4 (1H, d), 7.6 (1H, s), 8.2 (1H, d).

7) **7-Chloro-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (CH_2Cl_2/ MeOH: 9/1) afforded the title compound as a yellow solid (1.14 g, 89%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.52 min. *m/z* = 222 (M + 2).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.3 (2H, q), 3.2 (2H, t), 4.2 (2H, t), 7.6 (2H, q), 8.3 (1H, s).

8) **8-Chloro-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (CH_2Cl_2/ MeOH: 9/1) afforded the title compound as a yellow solid (0.97g, 75%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.30 min. *m/z* = 222 (M + 2).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.3 (2H, q), 3.2 (2H, t), 4.2 (2H, t), 7.4 (1H, m), 7.6 (2H, m).

9) **8-Trifluoromethyl-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one**

A mixture of 2-amino-6-trifluoromethyl-benzoic acid (0.97 g), 2-methoxypyrroline (0.703 g, 1.5 eq) in dry toluene (12 mL) was stirred at reflux for 3h. The orange solution was then evaporated to dryness to give a crude orange solid

FC (CH_2Cl_2/ MeOH: 9/1) afforded the title compound as a yellow powder (0.89g, 74%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.90 min. *m/z* = 255 (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.3 (2H, q), 3.2 (2H, t), 4.25 (2H, t), 7.75 (1H, t), 7.85 (2H, d).

C. 3-Bromo-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one derivatives

General procedure:

A mixture of a 2,3-Dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one derivative (1 eq), NBS (1 eq), AIBN (0.085 eq) in dry $CHCl_3$ (20 mL/ g) was stirred at reflux for 20 h under nitrogen. After cooling, the mixture was concentrated under reduced pressure, the resulting crude solid was purified by FC (AcOEt/ heptane: 7/3) to give the title compound.

1) **3-Bromo-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (AcOEt/ heptane: 7/3) afforded the title compound as brown crystals (40%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.49 min. *m/z* = 266 (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.55-2.8 (2H, m), 4.1-4.5 (2H, m), 5.3 (1H, d), 7.5 (1H, m), 7.7 (1H, m), 8.3 (1H, d).

2) **3-Bromo-5-fluoro-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (AcOEt/ heptane: 7/3) afforded the title compound as a n orange solid (35%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.77 min. *m/z* = 285 (M +2).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.6-2.85 (2H, m), 4.2-4.45 (2H, m), 5.35 (1H, d), 7.5 (2H, m), 8.1 (1H, d).

3) **3-Bromo-6-fluoro-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (AcOEt/ heptane: 7/3) afforded the title compound as a n orange solid (52%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.70 min. *m/z* = 284 (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.55-2.8 (2H, m), 4.1-4.5 (2H, m), 5.3 (1H, d), 7.2 (1H, m), 7.5 (1H, m), 8.3 (1H, m).

4) **3-Bromo-7-fluoro-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (AcOEt/ heptane: 7/3) afforded the title compound as a reddish solid (53%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.65 min. *m/z* = 284 (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.6-2.85 (2H, m), 4.2-4.5 (2H, m), 5.3 (1H, d), 7.5 (1H, m), 7.7 (1H, m), 7.95 (1H, m).

5) **3-Bromo-6,7-difluoro-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (AcOEt/ heptane: 7/3) afforded the title compound as a red solid (69%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 4.01 min. *m/z* = 302 (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.55-2.8 (2H, m), 4.05-4.5 (2H, m), 5.3 (1H, d), 7.5 (1H, m), 8.1 (1H, m).

6) **3-Bromo-6-chloro-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (AcOEt/ heptane: 7/3) afforded the title compound as a reddish solid (42%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 4.16 min. *m/z* = 300 (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.6-2.85 (2H, m), 4.1-4.5 (2H, m), 5.3 (1H, d), 7.5 (1H, dd), 7.7 (1H, s), 8.3 (1H, d).

7) **3-Bromo-7-chloro-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (AcOEt/ heptane: 7/3) afforded the title compound as a pink solid (49%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 4.12 min. *m/z* = 300 (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.55-2.85 (2H, m), 4.1-4.5 (2H, m), 5.3 (1H, d), 7.7 (2H, s), 8.3 (1H, s).

8) **3-Bromo-8-chloro-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one**

FC (AcOEt/ heptane: 7/3) afforded the title compound as a violet powder (38%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.56 min. *m/z* = 300 (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.55-2.85 (2H, m), 4.1-4.5 (2H, m), 5.3 (1H, d), 7.5 (1H, dd), 7.8 (2H, m).

9) 3-Bromo-8-trifluoromethyl-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one

FC (AcOEt/ heptane: 7/3) afforded the title compound as a red solid (36%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 4.47 min. *m/z* = 334 (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.55-2.85 (2H, m), 4.2-4.5 (2H, m), 5.3 (1H, d), 7.8 (1H, t), 7.9 (2H, m).

C. 3-(1-Phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one derivatives

General procedure

A mixture of a 3-bromo-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one derivative (0.56 g, 2.11 mmol), (D,L)-α-methylbenzylamine (1 eq), TEA (1.5 eq) in dry EtOH (10 mL), was stirred at reflux for 20h under nitrogen. After cooling, the reaction mixture was combined with CH_2Cl_2/ water and the aqueous phase was extracted twice with CH_2Cl_2. The combined extracts were dried (anhydrous $MgSO_4$), filtered and concentrated to give a dark green residue as mixture of diastereoisomers.

1) 3-(1-Phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one

FC (AcOEt/ heptane: 7/3) afforded the title compound as a dark green solid (69%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.00 min. *m/z* = 306 (M + 1).

2) 6-Fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one

FC (AcOEt/ heptane: 7/3) afforded the title compound as a dark oil (56%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.18 min. *m/z* = 324 (M + 1).

3) 7-Fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one

FC (AcOEt/ heptane: 7/3) afforded the title compound as a dark brown oil (62%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.06 min. *m/z* = 324 (M + 1).

4) 6,7-Difluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one

FC (AcOEt/ heptane: 7/3) afforded the title compound as a dark green oil (42%).

LC-MS (MeCN/ H_2O: 1/1): $R_t = 3.31$ min. $m/z = 342$ (M + 1).

5) 6-Chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one

FC (AcOEt/ heptane: 7/3) afforded the title compound as a dark green oil (50%).

LC-MS (MeCN/ H_2O: 1/1): $R_t = 3.40$ min. $m/z = 340$ (M + 1).

6) 7-Chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one

FC (AcOEt/ heptane: 7/3) afforded the title compound as a dark brown oil (54%).

LC-MS (MeCN/ H_2O: 1/1): $R_t = 3.34$ min. $m/z = 340$ (M + 1).

7) 8-Chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one

FC (AcOEt/ heptane: 7/3) afforded the title compound as a dark brown oil (71%).

LC-MS (MeCN/ H_2O: 1/1): $R_t = 3.21$ min. $m/z = 340$ (M + 1).

8) 3-((S)-1-Phenyl-ethylamino)-8-trifluoromethyl-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one

Reaction with the (S)-α-methylbenzylamine

FC (AcOEt) afforded the title compound as a dark brown oil (68%).

LC-MS (MeCN/ H_2O: 1/1): $R_t = 3.63$ min. $m/z = 374$ (M + 1).

9) 5-Fluoro-3-((S)-1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one

Reaction with the (S)-α-methylbenzylamine

FC (AcOEt) afforded the title compound as a dark green oil (58%).

LC-MS (MeCN/ H_2O: 1/1): $R_t = 3.36$ min. $m/z = 324$ (M + 1).

D. 6,7,8,9-Tetrahydro-pyrido[2,1-*b*]quinazolin-11-one derivatives

General procedure

To a suspension of 2-aminobenzoic acid derivative (1 eq) in dry $CHCl_3$ (20 mL/ g), was added slowly $POCl_3$ (1.3 eq) accompanied by stirring for 15 min at rt under nitrogen. Then δ-valerolactam (1.1 eq) was added portionwise over a period of 10 min, the reaction mixture was stirred at reflux under nitrogen for 3 h. Aqueous HCl 5% was added to the reaction mixture, the aqueous phase was separated (this operation was repeated three times). The combined aqueous extracts were clarified by adding active charcoal and filtered through celite. The resulting pale yellow solution was basified with concentrated aqueous ammoniac and extracted with CH_2Cl_2 (three times). The combined organic extracts were washed with water, dried (anhydrous Na_2SO_4), concentrated under reduced pressure to give a solid which was used for the next step without further purification.

1) 6,7,8,9-Tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

Light orange crystals (41%)

LC-MS (MeCN/ H_2O: 1/1): $R_t = 2.83$ min. $m/z = 201$ (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.00 (4H, m), 3.1 (2H, t), 4.1 (2H, t), 7.5 (1H, t), 7.6-7.8 (2H, m), 8.3 (1H, d).

2) 3-fluoro-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

Yellow crystals (44%)

LC-MS (MeCN/ H_2O: 1/1): $R_t = 3.34$ min. $m/z = 219$ (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.00 (4H, m), 3.0 (2H, t), 4.1 (2H, t), 7.1 (1H, m), 7.2 (1H, d), 8.3 (1H, t).

3) 2-fluoro-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

Yellow solid (56%)

LC-MS (MeCN/ H_2O: 1/1): $R_t = 3.39$ min. $m/z = 219$ (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.00 (4H, m), 3.0 (2H, t), 4.1 (2H, t), 7.4 (1H, m), 7.6 (1H, m), 7.9 (1H, dd).

4) 2,3-Difluoro-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

Yellow crystals (45%)

LC-MS (MeCN/ H_2O: 1/1): R_t =3.82 min. *m/z* = 237 (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.00 (4H, m), 2.95 (2H, t), 4.1 (2H, t), 7.35 (1H, q), 8.0 (1H, t).

E. 6-Bromo-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one derivatives

These compounds have been prepared as described for the 3-bromo-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one derivatives.

1) 6-Bromo-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

Pale yellow crystals (55%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.86 min. *m/z* = 280 (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.1-2.6 (4H, m), 4.00 (1H, m), 4.4 (1H, m), 5.4 (1H, s), 7.5 (1H, t), 7.7 (2H, m), 8.3 (1H, d).

2) 6-Bromo-3-fluoro-6,7,8,9-Tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

Pale yellow crystals (65%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 4.21 min. *m/z* = 298 (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.1-2.6 (4H, m), 4.00 (1H, m), 4.4 (1H, m), 5.4 (1H, s), 7.2-7.5 (2H, m), 8.3 (1H, d).

3) 6-Bromo-2-fluoro-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

White solid (69%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 4.20 min. *m/z* = 298 (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.1-2.6 (4H, m), 4.00 (1H, m), 4.4 (1H, m), 5.35 (1H, s), 7.5 (1H, m), 7.7 (1H, m), 7.9 (1H, dd).

4) 6-Bromo-2,3-difluoro-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

White solid (55%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 4.49 min. *m/z* = 316 (M + 1).

^{1}H-NMR (300MHz; $CDCl_3$) δ 2.1-2.6 (4H, m), 3.95 (1H, m), 4.4 (1H, m), 5.35 (1H, s), 7.45 (1H, t), 8.05 (1H, t).

F. 6-(1-Phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one derivatives

These compounds have been prepared as decribed for the 3-(1-phenyl-ethylamino)-2,3-dihydro-1*H*-pyrrolo[2,1-*b*]quinazolin-9-one derivatives (mixture of diastereoisomers).

1) 6-(1-Phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

Pale yellow solid (72%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 2.98 and 3.19 min. *m/z* = 320 (M + 1).

2) 3-Fluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

Yellow solid (40%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.18 min. *m/z* = 338 (M + 1).

3) 2-Fluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

Yellow solid (26%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.14 min. *m/z* = 338 (M + 1).

4) 2,3-Difluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one

Yellow solid (40%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 3.15 min. *m/z* = 356 (M + 1).

Example 1

1-(9-Oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea (mixture of diatereoisomers)

To a solution of 3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (50 mg, 0.163 mmol) in dry CH_2Cl_2 (1 mL), was added 2-n-propylphenyl isocyanate (26.3 mg, 0.163 mmol). The resulting reaction mixture was stirred at rt under nitrogen for 20h. The reaction mixture was then concentrated under reduced pressure and the residue was

purified by FC (AcOEt/ heptane: 7/3) to give the title compound as a white foam (45%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 3.00 min. *m/z* = 467 (M + 1).

Example 2

3-Biphenyl-2-yl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea (mixture of diatereoisomers)
In analogy to Example 1 using with 2-biphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a white foam (63%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 4.89 and 5.49 min. *m/z* = 500 (M).

Example 3

3-(2-Ethoxy-phenyl)-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea (mixture of diatereoisomers)
In analogy to Example 1 using 2-ethoxyphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a white foam (55%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 4.60 and 5.23 min. *m/z* = 468 (M).

Example 4

3-(2-Ethyl-phenyl)-1-(6-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea (mixture of diatereoisomers)
In analogy to Example 1 using 6-fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-ethylphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a white foam (62%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 4.76 and 5.33 min. *m/z* = 470 (M).

Example 5

3-Biphenyl-2-yl-1-(6-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea (mixture of diatereoisomers)
In analogy to Example 1 using 6-fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-biphenylisocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a white foam (82%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 5.01 and 5.61 min. *m/z* = 518 (M).

Example 6

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 6-fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-n-propylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige powder (61%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 5.06 and 5.61 min. *m/z* = 484 (M).

Example 7

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 6-fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-trifluoromethoxyphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a white solid (72%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 4.92 and 5.61 min. *m/z* = 526 (M).

Example 8

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-isopropyl-phenyl)-1-(1-phenyl-ethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 6-fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-isopropylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a white foam (70%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 4.98 and 5.48 min. *m/z* = 484 (M).

Example 9

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-naphthalen-1-yl-1(1-phenyl-ethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 6-fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 1-naphthyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a brown oil (77%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 4.72 and 5.28 min. *m/z* = 492 (M).

Example 10

1-(7-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-propyl-phenyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 7-fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-n-propylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as an orange oil (75%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 4.99 and 5.53 min. *m/z* = 484 (M).

Example 11

1-(7-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 7-fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-trifluoromethoxyphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a brown oil (83%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 4.85 and 5.52 min. *m/z* = 526 (M +1).

Example 12

3-Biphenyl-2-yl-1-(7-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 7-fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-biphenylisocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a yellow brown oil (70%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 5.02 and 5.59 min. *m/z* = 518 (M).

Example 13

3-(2-Ethyl-phenyl)-1-(7-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 7-fluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-ethylphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (70%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 4.77 and 5.32 min. *m/z* = 470 (M).

Example 14

3-Biphenyl-2-yl-1-(6,7-difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 6,7-difluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-biphenylisocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a pale grey foam (56%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 5.27 and 5.84 min. *m/z* = 536 (M).

Example 15

1-(6,7-Difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 6,7-difluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-trifluromethoxyphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a brown foam (61%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 5.07 and 5.74 min. *m/z* = 544 (M).

Example 16

1-(6,7-Difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 6,7-difluoro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-n-propylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a brown foam (67%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 5.22 and 5.74 min. *m/z* = 502 (M).

Example 17

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 7-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-ethylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a pale beige foam (66%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 5.09 and 5.73 min. *m/z* = 487 (M).

Example 18

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-naphthalen-1-yl-1(1-phenyl-ethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 7-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 1-naphthyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige solid (47%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 4.99 and 5.61 min. *m/z* = 509 (M).

Example 19

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-isopropyl-phenyl)-1-(1-phenyl-ethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 7-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-isopropylphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a grey solid (87%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 5.30 and 5.81 min. *m/z* = 501 (M).

Example 20

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 7-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-n-propylphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a white foam (58%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 5.34 and 5.92 min. *m/z* = 501(M).

Example 21

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 7-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-trifluoromethoxyphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a pale brown foam (74%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 5.18 and 5.92 min. *m/z* = 542 (M).

Example 22

3-Biphenyl-2-yl-1-(7-chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 7-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-biphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a white foam (72%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 5.36 and 5.99 min. *m/z* = 535 (M).

Example 23

3-Biphenyl-2-yl-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-biphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a yellow oil (22%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 4.99 and 5.80 min. *m/z* = 515 (M + 1).

Example 24

1-(11-Oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-n-propylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (53%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 5.18 and 5.86 min. *m/z* = 481 (M + 1).

Example 25

3-(2-Ethyl-phenyl)-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-ethylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a yellow oil (72%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 4.87 and 5.54 min. *m/z* = 467 (M + 1).

Example 26

3-(2-Ethoxy-phenyl)-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-ethoxyphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige solid (41%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 4.81 and 5.67 min. *m/z* = 483 (M + 1).

Example 27

3-Naphthalen-1-yl-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea (mixture of diatereoisomers)
In analogy to Example 1 using 6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 1-naphthyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige solid (28%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 4.87 and 5.51 min. *m/z* = 489 (M + 1).

Example 28

1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea (mixture of diatereoisomers)
In analogy to Example 1 using 2,3-difluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-n-propylphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (80%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 6.13 min. *m/z* = 517 (M + 1).

Example 29

3-Biphenyl-2-yl-1-(2,3-difluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenylethyl)-urea (mixture of diatereoisomers)
In analogy to Example 1 using 2,3-difluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-biphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (48%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 5.57and 6.22 min. *m/z* = 551 (M + 1).

Example 30

1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 2,3-difluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-ethylphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (97%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 5.35 and 5.92 min. *m/z* = 503 (M + 1).

Example 31

1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-3-(2-ethoxy-phenyl)-1-(1-phenyl-ethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 2,3-difluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-ethoxyphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (60%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 5.22 and 6.07 min. *m/z* = 519 (M + 1).

Example 32

3-Biphenyl-2-yl-1-(3-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenylethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 3-fluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-biphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (42%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 5.38 and 6.10 min. *m/z* = 533 (M + 1).

Example 33

1-(3-Fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 3-fluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-n-propylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (98%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 5.29 and 5.96 min. *m/z* = 499 (M + 1).

Example 34

3-(2-Ethoxy-phenyl)-1-(3-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenylethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 3-fluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-ethoxyphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a foam (88%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 5.03 and 5.93 min. *m/z* = 501 (M + 1).

Example 35

3-(2-Ethyl-phenyl)-1-(3-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenylethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 3-fluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-ethylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a foam (47%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 5.07 and 5.74 min. *m/z* = 485 (M + 1).

Example 36

3-Biphenyl-2-yl-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenylethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 2-fluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-biphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a yellow powder (43%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 5.38 and 6.07 min. *m/z* = 533 (M + 1).

Example 37

1-(2-Fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 2-fluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-n-propylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as an orange-brown powder (53%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 5.29 and 5.94 min. *m/z* = 499 (M + 1).

Example 38

3-(2-Ethoxy-phenyl)-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenylethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 2-fluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-ethoxyphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a yellow powder (44%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 5.03 and 5.86 min. *m/z* = 501 (M + 1).

Example 39

3-(2-Ethyl-phenyl)-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenylethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 2-fluoro-6-(1-phenyl-ethylamino)-6,7,8,9-tetrahydro-pyrido[2,1-*b*]quinazolin-11-one (1 eq) and 2-ethylphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a yellow powder (54%).

LC-MS (MeCN/ H_2O: 1/1): R_t = 5.07 and 5.72 min. *m/z* = 485 (M + 1).

Example 40

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 8-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-trifluoromethoxyphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a white foam (74%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 4.97 and 5.74 min. *m/z* = 542 (M).

Example 41

3-Biphenyl-2-yl-1-(8-chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 8-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-biphenylisocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a yellow foam (70%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 5.16 and 5.80 min. *m/z* = 535 (M).

Example 42

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-isopropyl-phenyl)-1-(1-phenyl-ethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 8-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-isopropylphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (70%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 5.11 and 5.67 min. *m/z* = 501 (M).

Example 43

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-naphthalen-1-yl-1(1-phenyl-ethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 8-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 1-naphthyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (57%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 4.83 and 5.46 min. *m/z* = 509 (M).

Example 44

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 8-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-n-propylphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (64%).
LC-MS (MeCN/ H_2O: 1/1): R_t = 5.11 and 5.74 min. *m/z* = 501(M).

Example 45

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea (mixture of diatereoisomers)

In analogy to Example 1 using 8-chloro-3-(1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-ethylphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a pale beige foam (83%).
LC-MS (MeCN/ H_2O: 1/1): R_t =4.86 and 5.53 min. *m/z* = 486 (M).

Example 46

1-(5-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea

In analogy to Example 1 using 5-fluoro-3-((S)1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-n-propylphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a pale beige foam (57%).
LC-MS (MeCN/ H_2O: 1/1): R_t =5.27 and 5.74 min. *m/z* = 485 (M + 1).

Example 47

3-Biphenyl-2-yl-1-(5-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-urea

In analogy to Example 1 using 5-fluoro-3-((S)1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-biphenyl isocyanate (1 eq).

FC (AcOEt/ heptane: 7/3) afforded the title compound as a green foam (73%).
LC-MS (MeCN/ H_2O: 1/1): R_t =5.39 and 5.94 min. *m/z* = 519 (M + 1).

Example 48

1-(5-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea

In analogy to Example 1 using 5-fluoro-3-((S)1-phenyl-ethylamino)-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-trifluoromethoxyphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a pale green solid (62%).
LC-MS (MeCN/ H_2O: 1/1): R_t =5.13 and 5.72 min. *m/z* = 527 (M + 1).

Example 49

1-(9-Oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea

In analogy to Example 1 using 3-((S)-1-Phenyl-ethylamino)-8-trifluoromethyl-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-trifluoromethoxyphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (68%).
LC-MS (MeCN/ H_2O: 1/1): R_t =5.39 and 6.14 min. *m/z* = 577 (M + 1).

Example 50

1-(9-Oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea

In analogy to Example 1 using 3-((S)-1-Phenyl-ethylamino)-8-trifluoromethyl-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-n-propylphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (54%).
LC-MS (MeCN/ H_2O: 1/1): R_t =5.54 and 6.13 min. *m/z* = 535 (M + 1).

Example 51

3-(2-Ethyl-phenyl)-1-(9-oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-urea

In analogy to Example 1 using 3-((S)-1-Phenyl-ethylamino)-8-trifluoromethyl-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-ethylphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (62%).
LC-MS (MeCN/ H_2O: 1/1): R_t =5.34 and 5.96 min. *m/z* = 521 (M + 1).

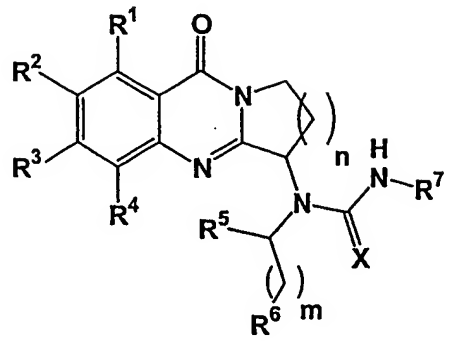
Example 52

3-Biphenyl-1-(9-oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-urea

In analogy to Example 1 using 3-((S)-1-Phenyl-ethylamino)-8-trifluoromethyl-2,3-dihydro-*1H*-pyrrolo[2,1-*b*]quinazolin-9-one (1 eq) and 2-biphenyl isocyanate (1 eq).
FC (AcOEt/ heptane: 7/3) afforded the title compound as a beige foam (72%).
LC-MS (MeCN/ H_2O: 1/1): R_t =5.64 and 6.22 min. *m/z* = 569 (M + 1).

Claims

1. Compounds of the general formula (I)



formula (I)

wherein:

X is O or S;

n is the integer 1, 2, or 3;

m is the integer 0, 1, 2, 3;

R^1, R^2, R^3, R^4 independently represent cyano, nitro, halogen, hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, trifluoromethyl, trifluoromethoxy, cycloalkyloxy, aryloxy, aralkyloxy, heterocyclyloxy, heterocyclylalkyloxy, R^8CO-, N $R^9R^{10}CO$-, $R^9R^{10}N$-, R^8OOC-, R^8SO_2NH-, R^{11}-CO-NH- or R^2 and R^3 together or R^1 and R^2 together or R^3 and R^4 together may form with the phenyl ring a five, six or seven-membered ring containing one or two oxygen atoms which are separated by at least one carbon atom.

R^5 represents aryl, aralkyl, lower alkyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl;

R^6 represents hydrogen, lower alkyl, trifluoromethyl, -$(CH_2)_m$-OH, -$(CH_2)_m$-O-lower alkyl, -$(CH_2)_m$-CO_2H, -$(CH_2)_m$-CO_2-lower alkyl, -$(CH_2)_m$$CONH_2$, -$(CH_2)_m$-CONH-lower alkyl, or -$(CH_2)_m$-CON-(lower alkyl)$_2$, or -$(CH_2)_m$-N-(lower alkyl)$_2$;

R^7 represents aryl, aralkyl, lower alkyl, lower alkenyl, cycloalkyl, cycloalkyl-lower alkyl, heterocyclyl or heterocyclyl-lower alkyl;

R^8 represents lower alkyl, aryl, aralkyl, heterocyclyl or heterocyclyl-lower alkyl;

$R^9$and R^{10} independently represent hydrogen, alkyl, cycloalkyl, cycloalkyl-lower alkyl, aryl, aralkyl, heterocyclyl or heterocyclyl-lower alkyl;

R^{11} represents lower alkyl, aryl, cycloalkyl, heterocyclyl, $R^9R^{10}N$- or R^8O-.

and optically pure enantiomers, mixtures of enantiomers, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts thereof.

2. Compounds of the general formula I, wherein n is the integer 1 or 2, m is the integer 0, 1 or 2, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 have the meaning given in the formula I above and X represents oxygen.

3. Compounds of the general formula I wherein n is the integer 1 or 2, m is the integer 0, R^5 represents methyl, R^6 represents phenyl, R^1, R^2, R^3, R^4, and R^7 have the meaning given in the formula I above and X represents oxygen.

4. A compound according to any one of claims 1 to 3, selected from the group consisting of

1-(9-Oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

3-Biphenyl-2-yl-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-(2-Ethoxy-phenyl)-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-(2-Ethyl-phenyl)-1-(6-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-Naphthalen-1-yl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-(2-Ethyl-phenyl)-1-(6-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-Biphenyl-2-yl-1-(6-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-propyl-phenyl)-urea;

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-isopropyl-phenyl)-1-(1-phenyl-ethyl)-urea;

1-(6-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-naphthalen-1-yl-1(1-phenyl-ethyl)-urea;

1-(7-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(7-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

3-Biphenyl-2-yl-1-(7-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

3-(2-Ethyl-phenyl)-1-(7-fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

1-(6-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-naphthalen-1-yl-1(1-phenyl-ethyl)-urea;

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-isopropyl-phenyl)-1-(1-phenyl-ethyl)-urea;

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(7-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

3-Biphenyl-2-yl-1-(7-chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

3-Biphenyl-2-yl-1-(8-chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-isopropyl-phenyl)-1-(1-phenyl-ethyl)-urea;

1-(8-Chloro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-naphthalen-1-yl-1(1-phenyl-ethyl)-urea;

3-Biphenyl-2-yl-1-(6,7-difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-urea;

1-(6,7-Difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

1-(6,7-Difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(6,7-Difluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;

3-Biphenyl-2-yl-1-butyl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-urea;

1-Butyl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-3-(2-n-propyl-phenyl)-urea;

1-Benzyl-3-biphenyl-2-yl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-urea;

1-Benzyl-3-(2-ethoxy-phenyl)-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-urea;

1-Benzyl-1-(9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3yl)-3-(2-n-propyl-phenyl)-urea;

3-Biphenyl-2-yl-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

3-(2-Ethyl-phenyl)-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

3-(2-Ethoxy-phenyl)-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

3-Naphthalen-1-yl-1-(11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

3-Biphenyl-2-yl-1-(2,3-difluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-3-(2-ethyl-phenyl)-1-(1-phenyl-ethyl)-urea;

1-(2,3-Difluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-3-(2-ethoxy-phenyl)-1-(1-phenyl-ethyl)-urea;

3-Biphenyl-2-yl-1-(3-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

1-(3-Fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

3-(2-Ethoxy-phenyl)-1-(3-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

3-(2-Ethyl-phenyl)-1-(3-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

1-(2-Fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

3-(2-Ethyl-phenyl)-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

1-(2-Fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

3-(2-Ethoxy-phenyl)-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

3-Biphenyl-2-yl-1-(2-fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-1-(1-phenyl-ethyl)-urea;

1-(2-Fluoro-11-oxo-6,8,9,11-tetrahydro-7*H*-pyrido[2,1-*b*]quinazolin-6-yl)-3-naphthalen-1-yl-1-(1-phenyl-ethyl)-urea;

1-(5-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

3-Biphenyl-2-yl-1-(5-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-urea;

1-(5-Fluoro-9-oxo-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

1-(9-Oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-3-(2-trifluoromethoxy-phenyl)-urea;

1-(9-Oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-3-(2-n-propyl-phenyl)-urea;

3-(2-Ethyl-phenyl)-1-(9-oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-urea;

3-Biphenyl-1-(9-oxo-8-trifluoromethyl-1,2,3,9-tetrahydro-pyrrolo[2,1-*b*]quinazolin-3-yl)-1-((S)-1-phenyl-ethyl)-urea.

5. Pharmaceutical compositions for the treatment of disorders which are associated with the role of orexin, especially disorders such as obesity and sleep disorders, containing one or more compounds of any one of claims 1 to 4, or a pharmaceutically acceptable salt therof, and usual carrier materials and adjuvants.

6. The compounds of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, for use as medicaments for the treatment of disorders which are associated with a role of orexin, especially obesity, sleep disorders, cardiovascular disorders, cancer, pain, depression, schizophrenia or neurodegenerative disorders.

7. A method of treating or preventing diseases or disorders where an antagonist of a human orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound as claimed in any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof.

8. A process for the manufacture of pharmaceutical compositions for the treatment of disorders associated with the role of orexin, especially obesity, sleep disorders, cardiovascular disorders, cancer, pain, depression, schizophrenia or neurodegenerative disorders, containing one or more compounds as claimed in any one of claims 1 to 4, or a pharmaceutically acceptable salt or salts thereof, as active ingredients which process comprises mixing one or more active ingredient or ingredients with pharmaceutically acceptable excipients and adjuvants in a manner known per se.

9. Use of one or more compounds of any one of claims 1 to 4 in combination with other pharmacologically active compounds comprising other orexin receptor antagonists, lipid lowering agents, anorectic agents, sleep inducing agents, antidepressants or other drugs

beneficial for the prevention or treatment of disorders given in any one of claims 6 to 8.

10. A compound as described as end-product in any one of examples 1 to 63.

11. The invention as hereinbefore described.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 03/07297

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/519 C07D487/04 C07D471/04 A61P3/04 A61P25/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 47580 A (COULTON STEVEN ;JOHNS AMANDA (GB); PORTER RODERICK ALAN (GB); SMIT) 17 August 2000 (2000-08-17) cited in the application the whole document	1-10

[ ] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 September 2003	02/10/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schmid, J-C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/07297

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 7 and 9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 11
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 11

Present claim 11 is not clear in scope that a lack of clarity within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claim impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear, namely calims 1-10.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0047580 A	17-08-2000	AU 2910600 A	29-08-2000
		WO 0047580 A2	17-08-2000
		EP 1144409 A2	17-10-2001
		JP 2002536447 T	29-10-2002
		US 6596730 B1	22-07-2003